THE AMENDMENTS

In the Specification

Amend the paragraph starting at page 5, line 18:

The invention also provides novel pharmaceutical compositions comprising compounds of Formula Ia or Ib, which are highly selective antagonists of $P2Y_{12}$ receptors on platelets. The invention further provides a method of preventing or treating diseases or conditions associated with platelet aggregation; such diseases include venous thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, unstable angina, myocardial infarction, stroke, cerebral embolism, kidney embolisms and pulmonary embolisms.

Amend the paragraph starting at page 7, line 7:

C is [the] a carbon atom;

Amend the paragraph starting at page 7, line 8:

R_5, R_6, and R_7 are H, [[an]] alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl, such that the moiety defined according to Formula II is an ether; or

R_5, R_6, and R_7 are H, [[an]] alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl, such that the moiety defined according to Formula II is an ether; or
R_5 and R_6 are H, an alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl, and R_7 is alkoxy, cycloalkoxy, aralkyloxy, aryloxy, substituted aralkyloxy, or substituted aryloxy such that the moiety defined according to formula II is an acyclic acetal or ketal; or

Amend the paragraph starting at page 8, line 8:

~~O is~~ The two O-groups are the 2' and 3' oxygens of the furanose or carbocycle; and the 2' and 3' oxygens of the furanose or carbocycle are linked by a common carbon atom (C) to form a cyclical acetal, cyclical ketal, or cyclical orthoester;

Amend the paragraph starting at page 8, line 17:

When present, the alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl and substituted aryl components of R_5 to ~~R_9may~~ R_9 may be generally defined as , but are not limited to, the following:

Amend the paragraph starting at page 9, line 17:

and linked to the phosphate chain via the 5' position of the furanose or carbocycle (dinucleoside polyphosphate with at least one of the 2, 3, 2' and 3' positions of the furanose or carbocycle modified);

Amend the paragraph starting at page 10, line 5

Further provisions are that when D_1 and D_2 are oxygen, the furanose is preferably in the ~~β-configuration;and~~ β-configuration; and that the furanose is most preferably in the β-D-configuration.

Amend the paragraph starting at page 10, line 7:

Preferred compounds of general Formula I are molecules whose structures fall within the definitions of Formula Ia ~~and~~ or Formula Ib:

Amend the paragraph starting at page 10, line 19:

X_1, X_2, and X_3= are independently O, NH, CH_2, CHF, CHCl, CF_2, **or** CCl_2;

Amend the paragraph starting at page 12, line 3:

B' is a purine or pyrimidine residue according to general Formulae IV and V;

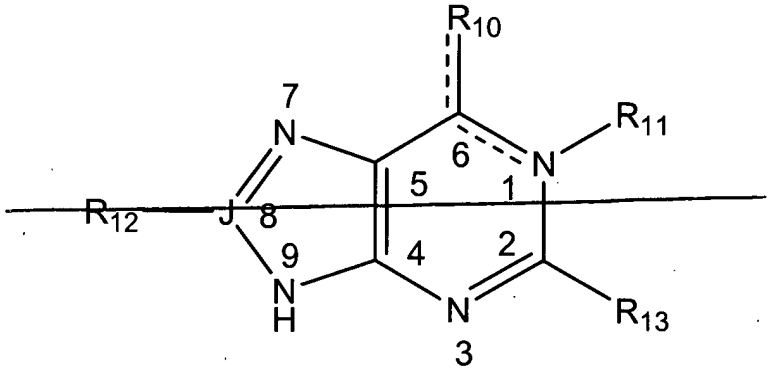
X_1 and X_2 are independently O, NH, CH_2, CHF, CHCl, CF_2, or CCl_2;

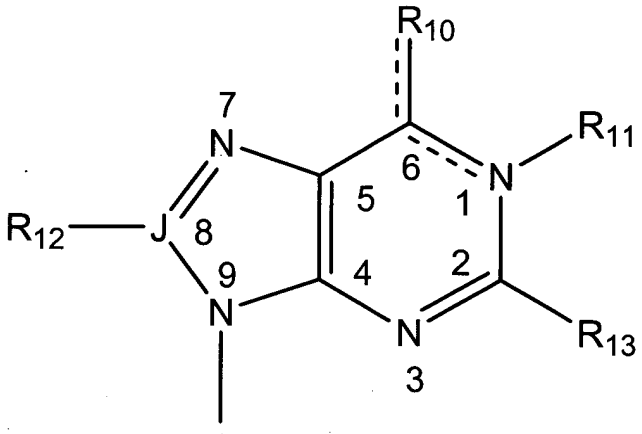
Amend the paragraph starting at page 12, line 28:

Z'= H, OH or OR_2, where R_1 and R_2 ~~falls~~ fall under the definition of general Formula II or III; with the proviso that at least one of Y' and Z' is OR_1 or OR_2, respectively.

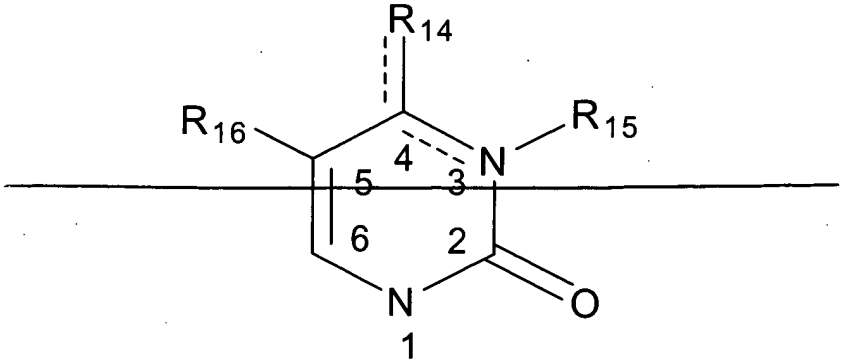
Amend the chemical structures on page 13, starting at line 3:

Formula IV

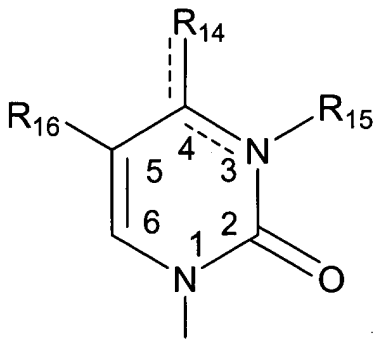




Formula V



Formula V



Amend the paragraph starting at page 14, line 25:

R_{17} is amino or mono- or disubstituted amino such that the moiety according to Formula VI is a urea or thiourea; ~~or~~R_{17} or R_{17} is alkoxy, aralkyloxy, aryloxy, substituted aralkyloxy, or substituted aryloxy, such that the moiety according to Formula VI is a carbamate or thiocarbamate; or

Amend the paragraph starting at page 15, line 16:

The compounds of the present invention may be prepared by derivatization or substitution at the level of the nucleoside, followed by phosphorylation and condensation as previously described, or the reactions may be carried out directly on the preformed mono- or dinucleotides. In the general Formulae Ia and Ib, the substituents at Y', Z', Y, and Z may be esters, carbamates, or carbonates, which are generally described by Formula II. Esters may be readily prepared by reacting a hydroxyl group of the furanose in a nucleoside or nucleotide with an activated form of an appropriate organic acid, such as an acid halide or acid ~~anyhydride~~ anhydride in the presence of an organic or inorganic base. Alternately, use of a suitable coupling reagent such as dicyclohexylcarbodiimide, 1,1'- carbonyldiimidazole and the like to activate the organic acid may be used to achieve the same result.

Amend the paragraph starting at page 17, line 10:

The inventors of the present invention have discovered compounds that are antagonists of the effect of ADP on its platelet membrane receptor, the $P2Y_{12}$ receptor. The compounds provide efficacy as antithrombotic agents by their ability to block ADP from acting at its platelet receptor site and thus prevent platelet aggregation. Thus, these compounds can provide a more efficacious antithrombotic effect than aspirin, but with less profound effects on bleeding than antagonists of the fibrinogen receptor. Since ADP-induced platelet aggregation is mediated by the simultaneous activation of both $P2Y_{12}$ and $P2Y_1$ receptors, the combined administration of the compounds described here with antagonists of platelet $P2Y_1$ receptors could potentially provide a more efficacious antithrombotic effect at concentrations of each antagonist that are below the effective concentrations to block each receptor subtype in other systems, resulting in a decrease of the potential manifestation of adverse effects. In addition, these compounds can be used in conjunction with lower doses of ~~these~~ other agents which inhibit platelet aggregation by different mechanisms, to reduce the toxicity of these agents. Finally, if the compounds of the present invention have sufficient binding affinity and bear a fluorescent moiety, they can find uses as biochemical probes for the $P2Y_{12}$ receptor.

Amend the paragraph starting at page 18, line 30:

[[A]] The method [of] includes treating a mammal to alleviate the pathological effects of atherosclerosis and arteriosclerosis, acute MI, chronic stable angina, unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis or abrupt closure following angioplasty, carotid endarterectomy, and anastomosis of vascular grafts.

Amend the paragraph starting at page 20, line 18:

For systemic administration such as injection and infusion, the pharmaceutical formulation is prepared in a sterile medium. The active ingredient, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Adjuvants such as local anesthetics, preservatives and buffering agents can also be dissolved in the vehicle. The sterile ~~indictable~~ injectable preparation may be a sterile ~~indictable~~ injectable solution or suspension in a

non-toxic acceptable diligent or solvent. Among the acceptable vehicles and solvents that may be employed are sterile water, saline solution, or Ringer's solution.

Amend the paragraph starting at page 20, line 29:

For oral use, an aqueous suspension is prepared by addition of water to dispersible powders and granules with a dispersing or wetting agent, suspending agent, one or more preservatives, and other excipients. Suspending agents include, for example, sodium carboxymethylcellulose, methylcellulose and sodium alginate. Dispersing or wetting agents include naturally-occurring phosphatides, condensation products of an allylene oxide with fatty acids, condensation products of ethylene oxide with long chain aliphatic alcohols, condensation products of ethylene oxide with partial esters from fatty acids and a hexitol, and condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anydrides. Preservatives include, for example, ethyl, and n-propyl p-hydroxybenzoate. Other excipients include sweetening agents (e.g., sucrose, saccharin), flavoring agents and coloring agents. Those skilled in the art will recognize the many specific excipients and wetting agents encompassed by the general description above.

Amend the paragraph starting at page 23, line 2:

The present invention also provides novel compositions of matter. The compositions are pharmaceutically acceptable formulations comprising compounds of Formula I of high purity, and/or in a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier can be selected by those skilled in the art using conventional criteria. The pharmaceutically acceptable carriers include, but are not limited to, saline and aqueous electrolyte solutions, water polyethers such as polyethylene glycol, polyvinyls such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, polymers of acrylic acid such as carboxypolymethylene gel, vegetable fats such as peanut oil and polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate and salts such as sodium chloride and potassium chloride.

Amend the paragraph starting at page 23, line 13:

Preferred compositions of the present invention ~~comprises~~ comprise compounds of Formula Ib (mononucleotide), provided that both X_1 and X_2 are not O, when n=1, and X_1 is not O when n=0; and provided that X_2 is ~~independently~~ O, CH_2, CHF, CHCl, CF_2, or CCl_2 when Y' = H; also provided that when $R_{10} = NH_2$ or O, and when R_5 and R_6 are taken together as oxygen doubly bonded to C, then R_7 is not equal to ortho-methylamino phenyl; further provided that when n=p=1, $X_2=CH_2$ and B'=adenosine, then R_1 and R_2 are not equal to napththylenylmethyl, napthylenylmethylene, or phenylmethylene.

Amend the paragraph starting at page 23, line 20:

Preferred compositions of the present invention also comprises compounds of Formula Ia, wherein B and B' are independently pyrimidine (pyrimidine/pyrimidine dinucleotide), provided that when m+n+p = 1, $R_{16} = CH_3$, and R_5 and R_6 are taken together as oxygen doubly bonded to C, then R_7 is not equal to CH_3 (Z' does not equal to acetate); also provided that when m+n+p = 3, B and B' = uridine, and R_5 and R_6 are taken together as oxygen doubly bonded to C, then R_7 is not equal to phenyl for Y'=OR_1 ~~and '~~ or Y= OR_4 (Y and Y' does not equal to benzoyl); further provided that when m+n+p = 1, then both R_8 and R_9 are not CH_3 (Z' and Y' taken together do not equal isopropylidine).

Amend the paragraph starting at page 23, line 28:

Preferred compositions of the present invention also ~~comprises~~ comprise compounds of Formula Ia, wherein B is a purine or residue according to general formula IV, and B' is a pyrimidine residue according to general formula V, (purine/pyrimidine dinucleotide); provided that Y' is not equal to OCH_3 when Z', Y, or [[Y]] Z = H or OH; further provided that R_8 is not equal to OCH_2CH_3 when R_9 = H (Z' and Y' or Z and Y taken together do not equal to an orthoethylester).

Amend the paragraph starting at page 24, line 3:

Preferred compositions of the present invention also ~~comprises~~ comprise compounds of

Formula Ia, wherein B and B' are independently a purine residue according to general formula IV, (purine/purine ~~dinonucleotide~~ dinucleotide); provided that ~~(a)Y~~ (a) Y or Y' is not equal to OCH_3 when $R_{10} = NH_2$ or O; (b) R_8 is not equal to OCH_3 or OCH_2CH_3 when R_9 = H; (c) both R_8 and R_9 are not equal to CH_3; (d) when m+n+p = 1, then R_8 and R_9 does not equal OCH_2CH_3; (e) when $R_{10} = NH_2$, and when R_5 and R_6 are taken together as oxygen doubly bonded to C, then R_7 is not equal to ortho-methylaminophenyl; (f) when m+n+p = 1, and when R_5 and R_6 are taken together as oxygen doubly bonded to C, then R_7 is not equal to $CH(CH_2CH_2SCH_3)NHS(o\text{-}NO_2\text{-}Ph)$ or $CH(CH_2Ph)NHS(o\text{-}NO_2\text{-}Ph)$.

Amend the paragraph starting at page 24, line 28:

Preferred composition also ~~comprises~~ comprise the following Compounds 1-21. In the following structures hydrogens which are understood to be present have been omitted for the sake of simplicity.

Amend the paragraph starting at page 35, line 16

~~1H~~ ^1H NMR (~~D2O~~ D_2O, 300 MHz): δ 4.10-4.47 (m, 4H), 5.17 (m, 1H), 5.83 (dd, 1H), 5.96 (m, 1H), 7.04 (t, 1H), 7.25 (m, 4H), 7.79 (m, 1H). ~~31P~~ ^{31}P NMR (~~D2O,121.47~~ D_2O, 121.47 MHz): δ -9.54 (m, 1P), -10.20 (m, 1P), -21.87 (m, 1P).

Amend the paragraph starting at page 36, line 30:

~~Tetraphenylcarbamate 1H~~ Tetraphenylcarbamate: ^1H NMR (D_2O, 300 MHz): δ 7.75 (d, 2H), 7.11 (m, 16H), 6.94 (m, 4H), 5.95 (d, 2H), 5.80 (d, 2H), 5.32 (m, 2H), 5.23 (m, 2H), 4.42 (m, 2H), 4.25 (m, 2H), 4.16 (m, 2H). ^{31}P NMR (D_2O, 121.47 MHz):): δ -10.30 (m, 2P), -22.32 (m, 2P).

Amend the paragraph starting at page 40, line 21:

~~**P^1-(4-N-(4-methoxyphenyl)aminocarbonylcytidine 5'-) -P^4-(uridine 5'-) tetraphosphate**~~

P^1-(N^4-(4-Methoxyphenyl)aminocarbonylcytidine 5'-)P^4-(uridine 5'-) tetraphosphate

~~P^1-(cytidine 5'-) -P^4~~ P^1-(Cytidine 5'-) P^4-(uridine 5'-) tetraphosphate, ditributylammonium salt (50 mg, 0.043mmol; prepared from the tetraammonium salt by

treatment with Dowex 50Wx4 H^+ in water, followed by mixing the protonated species with an excess of tributylamine in methanol, stripping and lyophilization) was dissolved in dry DMF (1mL) and tributylamine (10 uL, 0.43 mmol), and p-methoxyphenylisocyanate (8.4 uL, 0.648 mmol) were added in a single portion. The homogeneous reaction mixture was heated overnight at 35°C, whereupon TLC (silica gel, 50% isopropanol / 50% ammonium hydroxide) and HPLC (C18) indicated a substantial conversion to a single product. The solvent was removed on a rotary evaporator and the residue was dissolved in water (1mL). The product was isolated by repeated injections onto a semi-preparative HPLC column (Alltech Nucleotide/Nucleoside C18, 7um, 10 X 250 mm, gradient from 0.1 M ammonium acetate to methanol over 30 minutes, 5 mL/min, monitor at 260 nm). Stripping and lyophilization gave the p-methoxyphenylurea (24 mg, 55 % yield), as the tetraammonium salt.

Amend the paragraph starting at page 41, line 11:

P^1-(~~cytidine~~ Cytidine 5'-) [[-P^4]] P^4-(uridine 5'-) tetraphosphate, tetrasodium salt (500 mg, 0.57 mmol) was dissolved in water (5 mL) and a solution of 2,4'-dibromoacetophenone (792 mg, 2.85 mmol) in DMF (15 mL) added. The mixture was heated overnight at 40°C, and a further portion of the dibromoketone (400 mg, 1.44 mmol) in DMF (5 mL) added. The ~~rection~~ reaction was heated a further 5 hrs, and the solvents removed by evaporation. The residue was partitioned between water (20 mL) and ethyl acetate (25 mL) and the layers were separated. The aqueous layer was washed with further ethyl acetate (2x15 mL) and the aqueous was evaporated to dryness. The residue was dissolved in water (5 mL) and the product was isolated by repeated injections onto a semi-preparative HPLC column (see example 6 for conditions). The yield of the ~~pure~~ purified etheno compound was 80 mg (13.5%).

Amend the paragraph starting at page 41, line 26:

Example [[8]] 11 product was prepared from 100 mg P^1-(2'-deoxycytidine 5'-) -P^4-(uridine 5'-) tetraphosphate, tetrasodium salt and 2,4'-dibromoacetophenone, according to the general method of example [[7]] 10. Yield= 35 mg (30%).

Amend the paragraph starting at page 42, line 4:

Example [[9]] 12 product was prepared from 50 mg P^1,~~P4-Di~~ P^4-di(cytidine 5'-) tetraphosphate, tetrasodium salt and 2,4'-dibromoacetophenone, according to the general method of example [[7]] 10. Yield= 20 mg (29%).

^{1}H NMR (D_2O, 300 MHz): δ 4.24 (m, 10H), 5.98 (d, 2H), 6.39 (d, 2H), 7.14 (m, 8H), 7.45 (m, 4H).[[ ).]] ^{31}P NMR (D_2O, 121.47 MHz): δ -10.13 (m, 2P), -21.68 (m, 2P).

Amend the paragraph starting at page 42, line 11:

Example [[10]] 13 [[was]] product was prepared from 50 mg P^1,~~P4-Di~~ P^4-di(cytidine 5'-) tetraphosphate, tetrasodium salt and 2-bromo-4'-phenylacetophenone, according to the general method of example [7] 10. Yield= 15 mg (13%).

Amend the paragraph starting at page 42, line 18:

The products of examples ~~7-10~~ 10-13 can be further derivatized according to the methods of Examples 2-6, to give bifunctional molecules that fall within the scope of the invention.